REMARKS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herewith, which are believed to place the application into condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 48, 50 and 52-55 are pending in this application. Support for the recitation regarding the Notch ligand interacting with its receptor can be found throughout the specification. (See, for example, page 11, lines 5-7.) No new matter is added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art, and that these claims are and were in full compliance with the requirements of 35 U.S.C. §112. Amendments to the claims are not made for the purpose of patentability within the meaning of 35 U.S.C. §§§§101, 102, 103 or 112. Rather, these changes are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

II. THE REJECTIONS UNDER 35 U.S.C. §112, 1ST PARAGRAPH, ARE OVERCOME

Claims 48-51 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The rejection is traversed.

The Office Action admits that the specification is enabling for reducing T cell activation for allergic conditions, but states that it is not enabling for autoimmunity or the full spectrum of graft rejection. In view of the lengthy pendency of this application and in order to advance prosecution and minimize any remaining issues, the claims have been amended to remove autoimmunity, rendering that aspect of the rejection moot. However, there is no reason to expect that the demonstrated effects of administering a Notch ligand would not apply in the context of autoantigens. To the contrary, the examples presented in the instant description and in the Declarations under 37 CFR 1.132 that were previously presented during prosecuation are notable for their consistency, in that the same general reduction in immune response was seen with a wide variety of different antigens (for example a Der p I epitope in Examples 4, 5, 6 and 10 of the specification, hemagglutinin (HA) in Examples 7, 8 and 9 of the specification, ovalbumin in Example 4 of the specification, and a wide range of tissue antigens in Studies 1 and 2 of the Declaration by inventor Margaret J Dallman, filed on August 22, 2002). This very large and

varied range of examples indicates that the method of the present invention acts to reduce T-cell activation regardless of the particular antigen type involved.

The Office Action cites Jones *et al.* and Tufveson *et al.* in support of the allegation that different tissues are differently susceptible to T cell mediated rejection, and alleges that the skilled artisan would not know which types of graft rejection could be treated by administration of Delta or Serrate. Applicants disagree.

Jones *et al.* do disclose that heart, skin and pancreatic islet tissue are differentially susceptible to T cell-mediated allograft rejection. However, Jones *et al.* also emphasize that all such tissues are susceptible to T cell-mediated allograft rejection, thus giving reasonable grounds to expect that reduction of T-cell activation, as presently claimed, would provide a therapeutic benefit with all such tissues. Indeed, Jones *et al.* constantly refer to the role of T-cell activity in graft rejection, emphasizing the central role of T-cells in the last paragraph at page 2829, where they refer to "[t]he need for rigorous control of the alloreactive T-cell population ...". Thus, Jones *et al.* in fact emphasize the basic common role of T-cells in graft rejection. The distinction between tissues is simply one of degree.

The Office Action appears to have misquoted Tufveson *et al.*, in that the cited passage in fact states that "[a] main problem in the rodent model for organ allografting is the ease with which rejection is usually suppressed" (emphasis added). The general reference to "organ allografting" suggests that Tufveson *et al.* are not necessarily singling out cardiac tissue. Indeed, as stated by Jones *et al.*, heart tissue is by no means the least susceptible tissue to rejection, and Jones *et al.*, state in the Introduction that "pancreatic islets, vascularized pancreas, heart, kidney, and liver are progressively more easily accepted", indicating that heart grafts are by no means the most readily accepted. To the contrary, they have an intermediate position in the proposed hierarchy, which may well make them ideally suited as a model.

The present invention, as with the majority of treatments for graft rejection, seeks, first and foremost, to reduce rejection and prolong the life of the graft. This may or may not result in full acceptance or tolerance, but whether or not that is achieved, there is a reasonable expectation that a benefit will be realized by reducing T-cell activity, at least by prolonging graft survival. One might well expect some tissue types to be rejected more quickly or more easily than others, for the reasons discussed by Jones *et al.*, but that does not diminish the fact that, if T-cell activity is reduced, a general benefit in terms of graft survival is to be expected in all tissues.

The data provided in the present application shows that rejection of both cardiac tissue and lymphoid cells can be reduced by Notch signalling *in vivo*. Together with the data presented in relation to other antigens (Der p I, ovalbumin, HA etc.), it is submitted there is no reason to expect that T-cell activation against other allograft antigens would not also be reduced so as to reduce allograft rejection at least to some degree.

Claims 48-51 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The rejection is traversed.

The Office Action alleges that the specification is enabling for reducing T cell activation when Delta or Serrate are administered via recombinant cells or an F_c conjugate, but that it is not enabling for administration of Delta and Serrate by any other method. The Office Action goes on to state that "the present specification only provides a reasonable expectation of success where the Delta or Serrate is administered in such a manner where it can be expressed on the surface of an APC or T cell."

The data submitted in the Declaration by Brian R. Champion, filed on August 22, 2002, shows that Delta or Serrate signalling (on a plate or beads) was effective in modulating T-cell activation, in accordance with the invention as claimed (see Studies 1 and 3 of the Declaration). The Delta or Serrate protein is captured on the plate or beads, and is therefore not expressed on the surface of a cell, but a similar reduction of T-cell activation is still observed.

An additional Declaration by Dr. Champion is attached. In the experiments described in this Declaration, a fragment of Delta 1 comprising the DSL domain and the first three EGF-like repeats ("the Notch ligand") was delivered *in vivo* in two ways. In the first experiment, a reduction of T-cell activation was observed *in vivo* when the Notch ligand was conjugated to dextran and injected. A positive result was also observed in the second experiment, when the Notch ligand was coupled to iron oxide microbeads and injected. These results demonstrate that the Notch ligand need not be expressed on the surface of a recombinant cell or conjugated to an F_c domain In addition, functional language has been added to the claims to require that the Notch ligand interact with its receptor. This recitation excludes any inoperable embodiments of the invention.

Applicants have submitted a great deal of data during the prosecution of this application - both *in vitro* experiments that establish proof of principle, and *in vivo* experiments that demonstrate that the invention functions as claimed. Thus it is submitted that the specification is

enabled for the full scope of the claims, and reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, are requested.

CONCLUSION

In view of the remarks and amendments herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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